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**Original Research Article**

# Correlation of epidermal growth factor receptor score with prognostic variables in transitional cell carcinoma of urinary bladder among north-eastern Indian population

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## ABSTRACT

**Background:** Epidermal growth factor receptor (EGFR) has demonstrated over expression in bladder tumours and correlation with stage and grade of tumours. The aim of present study was to find the relation between score of the EGFR in Transitional Cell Carcinoma (TCC) of bladder and its various prognostic variables.
**Methods:** This is a retrospective study conducted in Dept of Urology, Gauhati Medical College Hospital between Dec 2016 and July 2017. Forty cases of TCC bladder that were operated either by TURBT or radical cystectomy have been taken. However, patients with CKD, pre-existing systemic disease and UTI were excluded from the study. Presence of EGFR and its score were analysed. The rating was done as 0 (non-immunoreactive), 1+ (weak), 2+ (moderate) and 3+ (strong). The correlation between EGFR score and the various factors like age, sex, stage, size of tumour, presence of CIS, tumour grade, muscle invasion, number of tumours and type of stalk were evaluated statistically using chi square tests.
**Results:** Average age is 59.825 years and male to female ratio is 5.6:1. EGFR score is not significantly related with age, sex, stage of disease, muscle invasiveness or number of tumours whereas size of tumour, presence of CIS changes, grade of TCC and type of tumour stalk bears statistically significant relation with EGFR score.
**Conclusions:** Studies have shown EGFR positivity to be associated with high tumour stage, tumour progression, and poor clinical outcome. Authors have found size >3cm, CIS changes, high grade tumours and broad-based stalks to be significantly associated with higher EGFR scores among patients with TCC of bladder.

**Keywords:** Epidermal growth factor receptor score, Prognostic variables, Transitional cell carcinoma bladder

## INTRODUCTION

Bladder cancer is the ninth most common cancer worldwide. A strong male to female predominance is seen, with over three-quarters of all bladder cancer cases occurring in men.[1] It is the seventh most common cancer in men and 17$^{th}$ in women.[2] In the United States and Western Europe, approximately 145,000 patients succumb from urinary bladder cancer worldwide per year.[2] The overall incidence rate of the urinary bladder cancer in India is 2.25% (per 100,000 annually) according to the reports of the National Cancer Registry Programme. Incidence among males is 3.67% and among females is 0.83%.[3] The north-eastern region of India is a known hub of various cancers and bladder cancer is no exception. Of late, there is surge in the incidence of bladder cancer population of northeast India. Approximately 70% of urinary bladder patients are non–

muscle invasive at presentation. Out of these, 70% present as stage Ta, 20% as T1, and only 10% as CIS.[4] The stage of presentation and the grade of tumour in bladder cancer determine the natural history. Prognosis is usually good in patients with non-muscle invasive tumour. Half of these patients shall be recurrence free at 5 years.[5] Of the rest 50%, 20% shall have experienced one recurrence, and the remaining 30% shall have multiple recurrences.[5,6] In the patients with recurrences, 50%–70% of tumours are of similar histological grade and stage as the primary tumour and in 20%-40% of patients, progression to muscle-invasive cancer occurs.[7,8] There are various factors that can predict the possibility of tumour recurrence like the presence of recurrent tumour in check cystoscopy at the three months, increase in tumour stage and grade, increase in tumour size, multifocality of tumour, presence of carcinoma in situ changes, and positive urine cytology.[9-11]

Dysregulation of the signalling systems of multiple growth factors and pro-inflammatory cytokines such as epidermal growth factor (EGF), transforming growth factor β and interleukin 6 (IL-6) are associated with cancer progression.[12-14] Among the members of the erbB tyrosine kinase receptors family, HER2/neu and EGF-receptor (EGFR), have been reported to be involved in the pathological processes of several cancer.[13]

Over expression of the protein product of the c-erbB-1 proto-oncogene, epidermal growth factor receptor (EGFR) has been associated with tumour progression in bladder cancers.[15-17] Various clinical studies have demonstrated that more than 50% of human TCCs express EGFR and the level of expression has a direct correlation with tumour grade, stage, and survival.[18] EGFR and its ligands promote the oncogenesis of many tumours of epithelial origin (breast, uterine cervix, bladder), and their expression of these factors are marker of poor prognosis.[19,20] This study was conducted with the aim to investigate upon the correlation of epidermal growth factor receptor score with prognostic variables in TCC bladder in Dept of Urology, Gauhati Medical College Hospital, Guwahati.

## METHODS

This is a retrospective study conducted in Dept of Urology and Renal Transplantation, Gauhati Medical College Hospital, Guwahati from Dec 2016 to July 2017. The patients of bladder tumour who underwent surgery in form of TURBT or radical cystectomy were evaluated for histopathology of the specimen. Those with transitional cell carcinoma were included in study. The patients who had non-transitional cell carcinoma such as with squamous differentiation, adenocarcinoma or others were excluded from study.

During cystoscopy the size of tumour/tumours (<3cm or ≥3cm), number of tumours (solitary/multiple), shape of stalk (whether broad based or papillary) were noted and the presence of suspected areas of carcinoma in situ changes were biopsied. After surgery the pathological examination was done in present Department of Pathology of present institute, the grade of tumor (high/low), muscle invasion (whether present or absent) and confirmation of CIS changes were reported. All the patients who had TCC bladder, their tumour block specimen were further evaluated with immunohistochemistry for the presence of EGFR and its score. The rating for presence of EGFR was done as 0 (non-immunoreactive), 1+ (weak), 2+ (moderate) and 3+ (strong). The correlation between EGFR score (0 /1+ /2+ /3+ ) and the various factors like age (<60years or ≥60 years), sex (male/female), stage (I/II/III/IV), size of tumour (< 3cm or ≥ 3cm), presence of CIS, grade (high/low), muscle invasion (presence or absence), number of tumours (solitary/multiple) and type of stalk (broad based/papillary) were evaluated. Statistical analyses were done using Pearson's Chi square analysis using software SPSS.

## RESULTS

There were 40 patients who had TCC of bladder, out of which 34 (85%) were male, and 6 others (15%) were female. Male to female ratio is 5.6:1. The mean age of the patients was 59.85±11.9 years.

**Table 1: Relation of age to EGFR score.**

| Age (years) | n | EGFR (0) | EGFR (1+) | EGFR (2+) | EGFR (3+) | p-value | Chi-square |
|---|---|---|---|---|---|---|---|
| <60 | 18 | 1 | 5 | 5 | 7 | 0.96429 | 0.277 |
| ≥60 | 22 | 2 | 5 | 6 | 9 | | |

**Table 2: Relation of sex to EGFR score.**

| Gender | n | EGFR (0) | EGFR (1+) | EGFR (2+) | EGFR (3+) | p-value | Chi-square |
|---|---|---|---|---|---|---|---|
| Male | 34 | 2 | 8 | 10 | 14 | 0.713 | 1.367 |
| Female | 6 | 1 | 2 | 1 | 2 | | |

Out of 40 patients, 3 patients were nonreactive for EGFR (graded as EGFR - 0) and rest of 37 patients were graded as EGFR 1+ (weak), 2+ (moderate) and 3+ (strong) immunoreactivity towards EGFR, in the specimen. The patients were divided into 2 age groups, more than 60 years or less than 60 years. EGFR score did not show any statistically significant correlation with both the age groups (p=0.96; Table 1) and gender (p=0.71; Table 2).

Patients were divided into two groups, those having tumour size more than or equal to 3 cm and those having less than 3 cm.

When comparing the EGFR score with these two groups, significant correlation was found with tumour size (p=0.03; Table 3), that is greater the size of tumour greater the chance of high EGFR score.

**Table 3: Relation of size of tumour and EGFR score.**

| Size of tumour | n | EGFR (0) | EGFR (1+) | EGFR (2+) | EGFR (3+) | p-value | Chi-square |
|---|---|---|---|---|---|---|---|
| <3cm | 17 | 3 | 6 | 5 | 3 | 0.0287 | 9.044 |
| >=3cm | 23 | 0 | 4 | 6 | 13 | | |

**Table 4: Relation of TNM stage with EGFR score.**

| Stage (AJCC TNM 2010) | n | EGFR (0) | EGFR (1+) | EGFR (2+) | EGFR (3+) | p-value | Chi-square |
|---|---|---|---|---|---|---|---|
| 1 | 20 | 3 | 7 | 5 | 5 | 0.3889 | 9.542 |
| 2 | 7 | 0 | 1 | 3 | 3 | | |
| 3 | 7 | 0 | 2 | 1 | 4 | | |
| 4 | 6 | 0 | 0 | 2 | 4 | | |

**Table 5: Relation of CIS with EGFR score.**

| CIS changes | n | EGFR (0) | EGFR (1+) | EGFR (2+) | EGFR (3+) | p-value | Chi-square |
|---|---|---|---|---|---|---|---|
| Yes | 21 | 0 | 2 | 5 | 14 | 0.00135 | 15.63 |
| No | 19 | 3 | 8 | 6 | 2 | | |

**Table 6: Relation of grade of TCC with EGFR score.**

| Grade | n | EGFR (0) | EGFR (1+) | EGFR (2+) | EGFR (3+) | p-value | Chi-square |
|---|---|---|---|---|---|---|---|
| Low | 17 | 3 | 7 | 4 | 3 | 0.01163 | 11.016 |
| High | 23 | 0 | 3 | 7 | 13 | | |

**Table 7: Relation of muscle invasiveness with EGFR score.**

| Muscle invasiveness | n | EGFR (0) | EGFR (1+) | EGFR (2+) | EGFR (3+) | p-value | Chi-square |
|---|---|---|---|---|---|---|---|
| Yes | 17 | 0 | 3 | 5 | 9 | 0.24735 | 4.134 |
| No | 23 | 3 | 7 | 6 | 7 | | |

**Table 8: Relation of number of tumours with EGFR score.**

| No of tumours | n | EGFR (0) | EGFR (1+) | EGFR (2+) | EGFR (3+) | p-value | Chi-square |
|---|---|---|---|---|---|---|---|
| Solitary | 14 | 3 | 4 | 2 | 5 | 0.067 | 7.148 |
| Multiple | 26 | 0 | 6 | 9 | 11 | | |

**Table 9: Relation of type of stalk with EGFR score.**

| Type of stalk | n | EGFR (0) | EGFR (1+) | EGFR (2+) | EGFR (3+) | p-value | Chi-square |
|---|---|---|---|---|---|---|---|
| Broad based | 25 | 0 | 4 | 8 | 13 | 0.018 | 10.051 |
| Papillary | 15 | 3 | 6 | 3 | 3 | | |

TNM staging was done and there were 20 patients with stage 1 disease, 7 patients with stage 2 disease, 7 patients with stage 3 disease and 6 patients with stage 4 disease.

Stage of presentation of bladder tumour did not have a statistically significant correlation (p=0.39; Table 4) with EGFR score. Carcinoma in situ changes in bladder were

determined by the positive biopsy of suspicious areas during TURBT. Authors found CIS in 21 patients. Presence of CIS changes along with bladder tumour showed a statistically significant correlation (p=0.001; Table 5) with EGFR score; that is presence of CIS has a predilection towards higher EGFR score.

Tumour specimens were graded as high grade or low grade (WHO classification,1998) according to the histologic features.[21] There were 23 patients with high grade tumours and 17 patients with low grade tumours. Authors found that grade of TCC is statistically significantly correlated (p=0.01; Table 6) with EGFR score; that is higher the grade higher the EGFR score.

Muscle invasion is defined as involvement of muscularis propria of bladder (AJCC 7th, 2010). There were 23 patients with NMIBC and 17 patients with MIBC. Authors found that muscle invasiveness of TCC has no significant correlation (p=0.25; Table 7) with EGFR score.

Authors found 14 patients to have solitary tumours and 26 patients to have multiple tumours. There was no statistically significant correlation (p=0.07; Table 8) of EGFR score with number of tumours whether solitary or multiple.

Twenty-five patients had broad based tumours while 15 patients had thin stalk. Authors found a statistically significant correlation (p=0.02; Table 9) with size of stalk whether broad based or thin with EGFR score.

## DISCUSSION

The epidermal growth factor receptor (EGFR/ErbB-1/HER1) is a transmembrane glycoprotein. It is a receptor for epidermal growth factor family of extracellular protein ligands.[22] It is a tyrosine kinase, which is encoded by a proto-oncogene located on chromosome 7p13. When epidermal growth factor (EGF) and transforming growth factor alpha (TGFα) binds to EGFR it results in down regulation of the receptor and stimulation of tyrosine kinase signaling pathways for cell migration, adhesion, and proliferation. Over expression of EGFR has an important role in promoting carcinogenesis.[23]

Present study population consist of patients with diverse ethnicity from different ethnicity from different regions of north east India where 92.5% of patients with TCC had positive EGFR score. Chow et al. observed EGFR over-expression in 72.2% of the patients among a pool of 245 patients with TCC.[24] Ravery et al. in their series of 43 cases of TCC, found EGFR over-expression in 86% of the patients.[25] Parvin et al. in their study of 57 cases of TCC found EGFR over expression in 86.9% of patients.[26]

In present study, EGFR score in TCC had not shown any statistically significant correlation with age (p=0.96) and gender (p=0.71). Parvin et al, in their study of 57 cases of TCC did not find any statistical correlation of EGFR status with sex (0.46) but found a significant relation with age (p=0.023). They found that in patients with over expression of EGFR, 28 (52.8%) patients were older than 60 years and 25 (47.2%) patients were 60 years or younger.[26] Kramer et al in his 121 patients of TCC did not find any significant correlation of gender with EGFR status.[27] Sriplakich et al found that, the groups with EGFR-positive and EGFR-negative bladder cancers were no different in respect to age and sex.[28]

In present study, authors have found a significant positive correlation (p value=0.03) with tumour size more than 3 cm with EGFR score. Chow et al. in his series of TCC bladder found significant association of tumour size with EGFR status (p value=0.026).[24] Neal et al in their 101 patients of bladder cancer, observed a significant association of tumour size with EGFR positivity in tumour specimen.[15]

In present study, authors found that multiplicity (number of tumours) had no statistically significant relation (p=0.67) with EGFR score while shape of tumour stalk had significant correlation (p=0.02). Chow et al in his 245 cases of primary transitional cell carcinoma of bladder, did not find significant association of number of tumours (p value=0.13) and shape of tumour (p value=0.813) with EGFR status.[24] However, Neal et al found significant association between multiplicity of tumour and EGFR status (p=<0.01).[15]

Authors have found that grade of tumour has a statistically significant association with EGFR score (p=0.01). Nguyen et al in their 85 patients with TCC of bladder, observed no significant association of EGFR score with grade of tumour (p>0.13).[29] Chow et al in his 245 cases of primary transitional cell carcinoma of bladder did not find significant association of grade of tumour with EGFR status (p= 0.145).[24] Similarly, Sriplakich et al found no relation between presence of EGFR and histological grade (p=0.56).[28] However, Kramer et al (p=0.046), Neal et al (p=<0.01) and Liukkonen et al found significant association between EGFR status and histologic grade of tumour.[15,27,30] In present study, authors have found statistically significant association of EGFR score with presence or absence of CIS changes (p=0.001). Both Bue et al and Ravery et al have found similar findings with CIS and EGFR status in their patients with TCC bladder.[25,31]

Authors had observed no significant association of muscle invasion of primary tumour (p=0.25) and stage of tumour (p=0.39) with the EGFR score in tumour specimens. Chow et al observed no significant correlation between EGFR status and TNM staging (p=0.291).[24] However, Kramer et al (p=<0.009), Sriplakich et al (p=0.015) and Neal et al (p=<0.01) have found statistically significant association between EGFR status and TNM staging of the disease.[15,27,28] Nguyen et al observed significant association of EGFR score with

tumour staging.[29] Recently, Parbin et al found no association between muscle invasion of TCC bladder and EGFR positivity (p=0.56). While Sriplakich et al found significant correlation of EGFR status with muscle invasiveness (p=0.015).[28]

Lipponen et al and Kramer et al in their multivariate analyses have found that EGFR status in TCC bladder is an independent factor predicting survival in patients.[16,27] Mellon et al found that EGFR status was found to be 80% sensitive and 93% specific in predicting stage progression in T1, grade 3 bladder cancer and concluded that it is a useful molecular marker in patients with bladder cancer, especially those in absence of infiltration of the detrusor muscle at presentation.[17]

Nicholson et al did a meta-analysis that has collected the results of more than 200 studies with nearly 20000 patients who suffered from several cancer types. They found relationship between survival and expression of EGFR and demonstrated EGFR over-expression was associated with reduced recurrence-free or overall survival rates in 70% of studies.[32]

Kassouf et al have shown that EGFR inhibitors have clear anti-proliferative and anti-angiogenic effects in preclinical models.[33] He demonstrated a potentiating effect of tyrosine kinase inhibitor, gefitinib on traditional chemotherapeutic agents in xenograft models.[34] Recently, Mosso et al has shown that prior chemotherapy rendered patients with muscle invasive TCC to be resistant to EGFR family inhibitors as well. However, EGFR family inhibitors may work well in those group of patients in whom no prior chemotherapy has been given and EGFR is over expressed.[35]

Urinary bladder TCC is emerging as a major health issue among elderly population of North East India, having diverse ethnicity. The EGFR correlation with various prognostic variables revealed that majority of patients (92.5%) with TCC of bladder expressed EGFR. The EGFR score has statistically significant association with prognostic factors like grade of tumour, size of tumour, presence of CIS and shape of stalk but not with age, gender, stage, muscle invasion and number of tumours. Over expression of EGFR in TCC of bladder makes this receptor a good therapeutic target. This one is the first study of correlation of EGFR with tumour variables among a distinct ethnic group of patients of north east India with wide diversity. The main limitation of this study is the low number of patients and no analysis on their follow up. Such a research study with more patients sample and proper follow up can throw some light on long term survival in two groups of patients of TCC (EGFR positive and its score versus EGFR negative). One of the important observations in this study is EGFR over expression among broad based tumours in comparison to tumours with thin stalk.

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